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Substituted Diphenylamines
Category Justification and Testing Rationale

CAS Nos. 68411-46-1, 68442-68-2, 184378-08-3, 101-67-7, 10081-67-1
36878-20-3, 68608-77-5 and 68921-45-9

Rubber and Plastic Additives Panel
American Chemistry Council
Revised August 2003

List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives (RAPA) Panel of the American Chemistry Council (ACC) includes the following member companies: Alco Chemical Corporation; Bayer Polymers LLC; Ciba Specialty Chemicals Corporation; Crompton Corporation; Eliokem, Inc.; Flexsys America L.P.; The Goodyear Tire & Rubber Company; The Lubrizol Corporation; Noveon, Inc.; and R.T. Vanderbilt Company, Inc.

Executive Summary

The ACC's RAPA Panel, and its member companies, hereby submit the revised category justification and test plan for the Substituted Diphenylamines category of chemicals under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Challenge Program. The category justification and test plan and the attached robust summaries in this submission are revisions of documents submitted in support of the Substituted Diphenylamines category on December 18, 2001. In revising these documents, comments received from EPA (dated November 27, 2002) and Environmental Defense (dated May 15, 2003) have been considered.

As discussed in the report that follows, Substituted Diphenylamines, which are used as antidegradants in rubber, foamed polymers and high-temperature functional fluids (lubricants, gear oils, hydraulic fluids), are defined as amines with various substitutions. Their use in these applications requires stability at high temperatures, low biodegradation, low water solubility and low vapor pressure.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted an extensive literature search for relevant available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information to address certain data requirements.

Substituted Diphenylamines Category

Relying on several factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program," in which use of chemical categories is encouraged, the following closely related chemicals constitute a chemical category:

Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)
Benzenamine, N-phenyl-, styrenated (68442-68-2)
Benzenamine, N-phenyl- (184378-08-3)[1]
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)

Structural Similarity. A key factor supporting the classification of these chemicals as a category is their structural similarity (see Figure 1). All share a common starting material; Diphenylamine (Benzenamine, N-phenyl-, CAS# 122-39-4), a common synthetic pathway, and all compounds in this category are diamines with various substitutions.

Similarity of Physicochemical Properties. The similarity of the physicochemical properties of these materials parallels their structural similarity. All are off-white to light brown solids or viscous liquids intended for use as antioxidants in finished rubber articles or as antidegradant additives that extend the useful life of heavy-duty industrial functional fluids used in high-speed, high-temperature and/or high-load applications. As a class, these amine-based antidegradant compounds are less migratory (more polymer-bound) and less staining than the Substituted p-Phenylenediamine antidegradants. The use of these materials requires that they be stable under high temperatures. Their low volatility is due to their low vapor pressure, highly viscous or solid form. The existing information for these materials indicates that they have low water solubility and high flash points.

Fate and Transport Characteristics. Members of this category have been shown to be not readily biodegradable, so additional testing is not needed. The lack of water solubility of the members of this category makes hydrolysis testing unnecessary. Adequate information regarding photodegradation is available for meeting HPV Program requirements; therefore, additional data collection efforts are not proposed. These materials have been shown not to partition to water or air if released into the environment due to their low water solubility and low vapor pressure. For the purposes of the HPV Program, additional computer-modeled environmental partitioning data is not necessary for the members of this category.

[1] A major component of CAS number 184378-08-3 is CAS number 68411-46-1.

Toxicological Similarity. Review of existing published and unpublished test data for Substituted Diphenylamines shows the aquatic and mammalian toxicity among the materials within this category are similar.

Aquatic Toxicology. Data on acute fish toxicity, acute invertebrate toxicity, and alga toxicity were reviewed. With increasing molecular weight, the toxicity to aquatic organisms decreases. These materials have high estimated log K_{ow} values, such that acute toxicity is not expected at or below their low levels of water solubility. For the purposes of the HPV Program, additional testing is not proposed for the members of this category.

Mammalian Toxicology - Acute. Data on acute mammalian toxicity were reviewed, and the findings indicate a low concern for acute toxicity for all materials. Data are available for most members of the category indicating that the category has been well tested for acute mammalian effects. Therefore, for the purposes of the HPV Program, no additional acute mammalian toxicity testing is proposed.

Mammalian Toxicology - Mutagenicity. Data from bacterial reverse mutation assays, *in vitro* and *in vivo* chromosome aberration studies, as well as additional supporting *in vitro* and *in vivo* genetic toxicity studies were reviewed, and the findings indicate a low concern for mutagenicity either for aryl or alkyl substituted materials. Similarly, the data for a mixed aryl/alkyl substituted molecule also indicates a lack of mutagenicity. Data are available for several members of the category or close structural analogs, and these data can be bridged to the other members of the category. Therefore, for the purposes of the HPV Program, the category has been adequately tested for mutagenicity, and no additional mutagenicity testing is proposed.

Mammalian Toxicology – Repeated Dose Toxicity. Data from repeated-dose toxicity studies were reviewed. Sufficient data are not available to adequately represent the Substituted Diphenylamines for the purposes of the HPV Program, and additional testing is proposed on the smallest aryl- and akyl-substituted materials.

Mammalian Toxicology - Reproductive and Developmental Toxicity. Data from reproductive and developmental toxicity studies were reviewed. Sufficient data are not available to adequately represent the Substituted Diphenylamines for the purposes of the HPV Program, and additional testing is proposed, and additional testing is proposed. It is proposed to test the smallest aryl- and akyl-substituted materials.

Conclusion. Based upon the data reviewed in the report, the physicochemical and toxicological properties of the Substituted Diphenylamine category members are similar and follow a regular pattern as a result of that structural similarity. Therefore, the EPA definition of a chemical category has been met.

As this test plan was developed, careful consideration was given to opportunities to minimize the need to generate new information using animal studies. In consideration of these and other concerns about animal welfare, the use of animals in the proposed test plan has been minimized. The test plan is included as Table 8 of this document.

Introduction

The category justification and test plan and the attached robust summaries in this submission are revisions of documents submitted in support of the Substituted Diphenylamines category on December 18, 2001. In revising these documents, comments received from EPA (dated November 27, 2002) and Environmental Defense (dated May 15, 2003) have been considered.

A provision for the use of structure activity relationships (SAR) to reduce testing needs is included under EPA's HPV Program. Specifically, categories may be formed based on structural similarity, through analogy, or through a combination of category and analogy for use with single chemicals. The benefits of using a category approach are numerous and include accelerated release of hazard information to the public; reduction in the number of animals used for testing; and an economic savings as a result of a reduced testing program.

The Substituted Diphenylamines materials that form this category based on structural similarity are:

Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)
Benzenamine, N-phenyl-, styrenated (68442-68-2)
Benzenamine, N-phenyl- (184378-08-3)[2]
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)

The materials were further arranged in order of molecular weight, so that the smallest material is listed first, and materials listed subsequently have increasingly larger molecular weights. All of these materials are listed under the HPV Program. Note that one chemical not included in the original submission has been added [Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (CAS number 10081-67-1)] and one original category member [Diphenylamine, 4, 4' –bis (1,1, 3, 3 – tetramethylbutyl)- (CAS number 15721-78-5)] is no longer sponsored by the RAPA Panel and has been removed.

Human exposure to diphenylamine derivatives that are used as rubber and oil antidegradants at levels of 5% or less is considered minimal as a pesticide and as an edible residue. In addition, three of the chemicals in this category (68411-96-1, 68442-68-2 and 101-67-7) have FDA approved uses.

The development of this category follows current EPA guidance[3].

[2] A major component of CAS number 184378-08-3 is CAS number 68411-46-1.
[3] US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. http://www.epa.gov/opptintr/chemrtk/categuid.htm.

Background Information: Manufacturing and Commercial Applications

Manufacturing

A common synthetic pathway in the production of Substituted Diphenylamines is via a process known as alkylation. The common starting material, diphenylamine, (or Benzenamine, N-phenyl-) is reacted with an olefin containing the desired substituent group(s). The resulting reaction product is typically purified by distillation.

Commercial Applications

Substituted Diphenylamines materials are highly effective and active antioxidants in natural and many types of synthetic rubbers. They also impart heat-resistance and flex-fatigue resistance to rubber articles used in high-temperature and dynamic applications, such as under-the-hood automotive belts, gaskets and bushings. Because of their relatively non-staining and non-migratory nature, some Substituted Diphenylamines are used in the manufacture of light-colored rubber articles and adhesives that may contact food. Typical use percentage for a Substituted Diphenylamine in rubber compounding is 1-4 parts for every 100 parts of rubber. In heavy-duty functional fluids, Substituted Diphenylamines are powerful antioxidants that extend the useful life of transmission fluids, gear oils, lubricants and hydraulic fluids that must retain their properties in high-speed, high-temperature and/or high-load applications. Typical use percentage for a Substituted Diphenylamine as a functional fluid antioxidant is 1-4%.

Because of their powerful antioxidant properties, Substituted Diphenylamines, along with their common starting material, Diphenylamine, are regulated for use in several food-contact applications by the Food and Drug Administration as Indirect Food Additives under the following sections of the Code of Federal Regulations (CFR):

21 CFR Section	Application	Approved Chemical (Substitituted Diphenylamines indicated by CAS number)
175.105	Components of Adhesives	Diphenylamine, 101-67-7 and 68422-68-2
175.300	Resinous and Polymeric Coatings	Diphenylamine
176.170	Components of Paper/Paperboard – Fatty Food	Diphenylamine
176.180	Components of Paper/Paperboard – Dry Food	Diphenyalmine
177.1210	Closures with Sealing Gaskets	68411-46-1
177.2600	Rubber Articles	Diphenylamine, 101-67-7
178.2010	Antioxidants/Stabilizers for Polymers	68411-46-1
178.3570	Lubricants with Food Contact	68411-46-1

Shipping/Distribution

Substituted Diphenylamines materials are shipped extensively throughout the world from manufacturing plants in the USA, Eastern and Western Europe and Japan. Container types vary with physical form, quantity of material and destination. Boxes, bags of varying sizes, drums, tote tanks and tank cars can be used to transport Substituted Diphenylamines.

Worker/Consumer Exposure

The rubber and plastics additives industry has a long safety record and sophisticated users handle materials. Exposure of workers handling Substituted Diphenylamine materials is likely to be the highest in the areas of material packaging at the manufacturing site and during raw material weigh-up at the customer site. These materials are produced as dust-suppressed powders, flakes, and viscous liquids. Thus, during the above operations, there is some potential for inhalation exposure (nuisance dust is the primary route of worker exposure) and dermal contact.

Development of the Substituted Diphenylamines Category

EPA has described a stepwise process for developing categories. These steps include:

- Grouping a series of like chemicals, including the definition of criteria for the group;
- Gathering data on physicochemical properties, environmental fate and effects, and health effects for each member of the category;
- Evaluating the data for adequacy;
- Constructing a matrix of available and unavailable data; and
- Determining whether there is a correlation among category members and data gathered.

Definition of the Substituted Diphenylamines Category

As defined by EPA under the HPV Program, a chemical category is "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional and unnecessary testing.

The materials within the Substituted Diphenylamines category, for the purposes of the HPV Program, are defined as amines, which vary with the degree of alkyl (straight chain or branched) or phenyl groups, as illustrated in Figure 1. These materials differ by the type and extent of the substitution of the phenyl group, with either alkyl or aryl substitution on the molecule, and in one instance, mixed alkyl/aryl substitution. Chemical structures for these materials are provided in Figure 2. The lack of water solubility, low vapor pressure, and inability to biodegrade are similar for the substituted diphenylamines (see Table 1). Furthermore, these materials are not flammable.

Matrix of SIDS Endpoints

In order to construct a matrix of SIDS endpoints for the members of the substituted diphenylamines category, the data on physicochemical properties, environmental fate and effects, and health effects for each member of the category must be collected and evaluated for adequacy. The results of these activities are presented in the tables and text below, providing a matrix of available data.

Correlation within the Substituted Diphenylamines Category

The matrix data patterns for physicochemical properties; environmental fate, ecotoxicity; and health effects have been evaluated for the members of the Substituted Diphenylamine category. A description of the results of this evaluation follows.

Correlation of Physicochemical Properties

The physicochemical properties of the members of the Substituted Diphenylamine category are presented in Table 2. These materials may exist as liquids or solids at room temperature, such that melting point or boiling point data may not be relevant for varying members of the category. The similarities in the other physicochemical properties of these materials, which are described below, are explained by similarities in their chemical structure, and provide justification of this group of chemicals as a category within the HPV Challenge Program.

The members of this category have a wide range of melting points and boiling points (varying based on the physical state as a liquid or solid). All the members of this category have very low vapor pressures, as indicated in Table 2. Data for the members of this category clearly indicate negligible water solubility. Partition coefficient data fall into two ranges, from ~4 to 6 and from ~10 to 12.

For the purposes of the HPV Program, bridging to other members of the category or testing will address outstanding physicochemical properties data requirements, as illustrated below.

- The vapor pressure for Benzenamine, 4-octyl-N-(4-octylphenyl) (101-67-7) will be bridged to:
    - Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3); and
    - Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]- (10081-67-1).
- The water solubility for Benzenamine, 4-octyl-N-(4-octylphenyl) (101-67-7) will be bridged to Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3).
- The partition coefficient for Benzenamine, 4-octyl-N-(4-octylphenyl) (101-67-7) will be bridged to:
    - Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3); and
    - Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]- (10081-67-1).
- The boiling point will be determined for:
    - Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3); and
    - Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]- (10081-67-1).
- The melting point will be determined for:
    - Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5);

- Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3); and
- Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9).

Correlation of Environmental Fate

The members of this category are found to be not readily biodegradable, have rapid photodegradation half-lives, and modeling shows a primary partitioning to soil and sediment fractions (vs. water) (Table 3). Hydrolysis data are not available for these materials, as discussed below.

The HPV Challenge Program requires that hydrolysis, photodegradation, biodegradation and environmental transport information be presented for each material or bridged to each member of a category. Adequate biodegradation data exist for the several of the materials in this category; bridging will be used to address the remaining biodegradation data requirements as illustrated below. As presented below, results indicate that these materials are poorly biodegradable. Hydrolysis testing of the members of this category is not appropriate since they are not water-soluble. Photodegradation studies presented for several members of this category are adequate; bridging will be used to fill the remaining photodegradation data requirements as illustrated below. Finally, fugacity modeling has been conducted on several of the members of this category, with consistent results showing partitioning to soil and sediment; with the exception noted above for diphenylamine. This is consistent with the lack of water solubility and low vapor pressure of these materials. For the purposes of the HPV Program, bridging to other members of the category will address outstanding environmental fate data requirements, as illustrated below.

- The photodegradation information from Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1) and Benzenamine, N-phenyl- (184378-08-3) will be bridged to:
  - Benzenamine, N-phenyl-, styrenated (68442-68-2); and
  - Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]-(10081-67-1).
- The photodegradation information from Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5) will be bridged to:
  - Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7); and
  - Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3).
- The biodegradation data from Benzenamine, N-phenyl-, styrenated (68442-68-2) and Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3) will be bridged to:
  - Benzenamine, N-phenyl- (184378-08-3);
  - Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7); and
  - Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]-(10081-67-1).
- The biodegradation data from Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3) will be bridged to:
  - Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5); and
  - Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9).

- Environmental Transport modeling will be bridged from Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1) to:
    - Benzenamine, N-phenyl-, styrenated (68442-68-2); and
    - Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]-(10081-67-1).
- Environmental Transport modeling will be bridged from Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5) to:
    - Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7); and
    - Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3).

Correlation of Ecotoxicity

The HPV Challenge Program requires that an acute aquatic ecotoxicity test in fish, invertebrates, and algae be performed or bridged to each member of a category. Existing data (Table 2) indicate that all members of the Substituted Diphenylamine category have low water solubility. The low water solubility suggests that the acute aquatic toxicity of these materials should be low due to limited bioavailability to aquatic organisms. These materials have high estimated log Kow values, such that acute toxicity is not expected at or below their water solubility. Sufficient data are available to meet HPV Program requirements for the toxicity of the Substituted Diphenylamines to aquatic organisms (Table 4). As the molecular weight of the category members increases, there is a clear reduction in the acute aquatic toxicity of these materials. For the purposes of the HPV Program, bridging from this data will be used to address the data information requirements for the remainder of this category as illustrated below.

- The data for Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7), Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1), Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3), and Benzenamine, N-phenyl-, styrenated (68442-68-2) will be bridged to the remaining members of this category.

Correlation of Health Effects

Acute Mammalian Toxicity

Acute oral and dermal toxicity data for the category are summarized in Table 5. Of the Substituted Diphenylamines tested, all show a slight to very low order of toxicity following oral administration, with LD_{50} values ranging from >500 to > 34,000 mg/kg. Overall, the acute dermal LD_{50} for these materials was greater than the 2000 mg/kg limit dose indicating a very low order of toxicity.

Numerous adequate acute toxicity studies have been conducted for the Substituted Diphenylamine category using two routes of exposure (oral and dermal); and the toxicity of four of the nine members of the category has been evaluated. The data demonstrate a slight to very low order of acute toxicity. The similarity in the order of toxicity for these materials is consistent with their similar chemical structure and physicochemical properties and supports the scientific justification of these materials as a category within the HPV Challenge Program.

The HPV Challenge Program requires that either an acute test be performed or bridged to each member of a category. Adequate acute oral toxicity tests exist for four of the Substituted Diphenylamines. For

the purposes of the HPV Program, bridging will be used to fill the remaining data requirements as follows.

- Acute oral toxicity data from Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1) will be bridged to Benzenamine, N-phenyl- (184378-08-3).
- Acute oral toxicity data from Benzenamine, N-phenyl-, styrenated (68442-68-2) will be bridged to Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1).
- Acute oral toxicity data from Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7) will be bridged to Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3).
- Acute oral toxicity data from Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5) will be bridged to Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9).

By bridging existing data to the materials for which data were not identified, the acute toxicity of the category has met requirements of the HPV Program with respect to all acute toxicity endpoints, and therefore, no additional acute toxicity testing is proposed.

Mutagenicity

A summary of the mutagenicity information for the Substituted Diphenylamines category is presented in Table 6. The weight of evidence for the members of this category indicates these materials are not mutagenic.

Adequate bacterial mutagenicity tests exist for five of the Substituted Diphenylamines category. For the purposes of the HPV Program, bridging will be used to address the remaining data requirements. Adequate *in vitro* chromosome aberration tests or *in vivo* micronucleus tests exist for two of the materials in the Substituted Diphenylamines category; bridging will be used to address the remaining data requirements. Bacterial and mammalian mutagenicity studies are available for aryl (for example, CAS No. 68442-68-2) and alkyl (for example, CAS No. 101-67-7) substituted diphenylamines. Furthermore, a bacterial mutagenicity study is also available for a mixed aryl/alkyl substituted phenylenediamine (CAS No. 68921-45-9). Each of these studies indicates a lack of mutagenicity of these materials, whether the substitution is alkyl (straight chain or branched), aryl or mixed alkyl/aryl.

Bacterial Gene Mutation Assay

Overall weight of evidence for the category indicates that the Substituted Diphenylamines are negative for bacterial mutagenicity.

In vitro or In vivo Chromosomal Aberration Assays

Two (one alkyl and one aryl substituted) of the Substituted Diphenylamine materials have been adequately tested in an in vitro or *in vivo* chromosomal aberration assay to satisfy HPV requirements. These test materials were negative for clastogenicity.

The Substituted Diphenylamines category has been evaluated for mutagenicity in tests for gene mutations and chromosomal aberrations. The assays included point mutations in bacterial cells, *in vitro* chromosomal aberrations in mammalian cells, and *in vivo* chromosomal aberrations. The data

consistently demonstrate no evidence of genotoxicity for this category of materials. This suggests that all members of the category lack genotoxicity due to their similarity in chemical structures and physicochemical properties. The similarity of results for genotoxicity supports treatment of these materials as a chemical category within the HPV Challenge Program.

The HPV Challenge Program requires that a gene mutation and a chromosomal aberration test be performed or bridged to each member of a category. For the purposes of the HPV Program, bridging will be used to address the remaining data requirements as follows.

- Bacterial and in vivo mammalian mutagenicity data will be bridged from Benzenamine, N-phenyl-, styrenated (68442-68-2) to Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1).
- Bacterial and in vitro mammalian mutagenicity data will be bridged from Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7) to:
    - Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3); and
    - Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1).
- In vitro mammalian mutagenicity data will be bridged from Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7) to:
    - Benzenamine, N-phenyl- (184378-08-3); and
    - Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5).
- In vivo and in vitro mammalian mutagenicity data will be bridged from Benzenamine, N-phenyl-, styrenated (68442-68-2) and Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7) to Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9).

By bridging these data, the category has met the requirements of the HPV Challenge Program, and therefore, no additional testing is proposed.

Repeat Dose Toxicity

A summary of the repeat dose toxicity data for the Substituted Diphenylamines category is presented in Table 7.

Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9) was tested in a 64-week rat dietary study; a LOEL of 2500 ppm was identified. Additional adequate repeat dose toxicity studies were not found for the remaining materials in this category. Additional repeat dose testing is proposed for the category to provide information on the smallest aryl and alkyl substituted molecules in the category, which is required for HPV Challenge purposes. Specifically, a 28-day repeat dose toxicity study with screening developmental and reproductive endpoints (OECD 422) is proposed for Benzenamine, N-phenyl-, styrenated (68442-68-2), which is the smallest aryl substituted compound and Benzenamine, N-phenyl- (184378-08-3), which is the smallest alkyl substituted compound in the category (as mentioned previously, a major component of CAS number 184378-08-3 is CAS number 68411-46-1).

Reproductive and Developmental Toxicity Standard reproductive and developmental toxicity data were not located for the Substituted Diphenylamine category (Table 7).

Adequate reproductive or developmental toxicity studies were not found for the materials in this category to meet HPV Program requirements. Additional testing is proposed to provide information on the smallest aryl and alkyl substituted molecules in the category, which is required for HPV Challenge purposes. Specifically, a 28-day repeat dose toxicity study with screening developmental and reproductive endpoints (OECD 422) is proposed for Benzenamine, N-phenyl-, styrenated (68442-68-2), which is the smallest aryl substituted compound and Benzenamine, N-phenyl- (184378-08-3), which is the smallest alkyl substituted compound in the category (as mentioned previously, a major component of CAS number 184378-08-3 is CAS number 68411-46-1).

Test Plan

Table 8 provides the category test plan for the Substituted Diphenylamines. Additional testing for the purposes of the HPV Program has been proposed for the chemicals that constitute the Substituted Diphenylamines category.

FIGURES

Figure 1. Substituted Diphenylamine Structural Definition

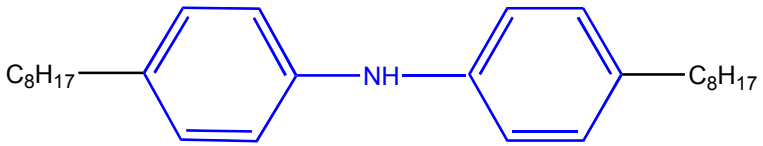
Mononitrogen (N) containing with various degrees of phenyl or alkyl substitution:

Ph-NH-Ph

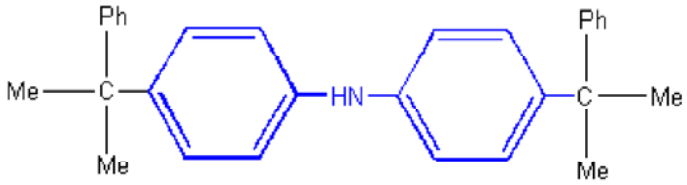
R-Ph-NH-Ph-R'

Where:
Ph = phenyl;
R,R' =butyl derivatives, octyl-derivatives, nonyl-derivatives, styrenyl-derivatives

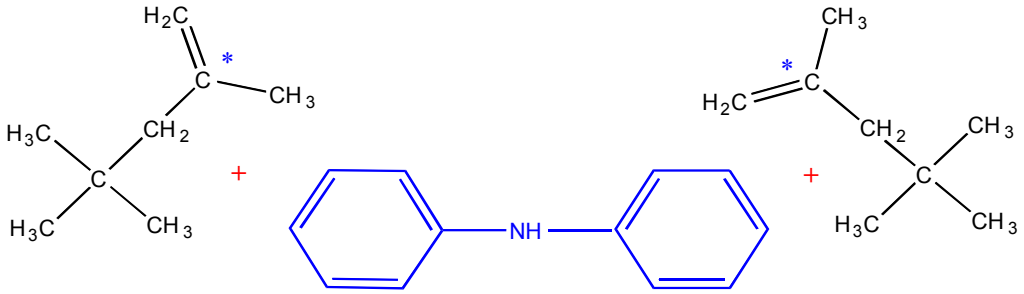
Figure 2 Substituted Diphenylamine Chemical Structures



101-67-7
Benzenamine, 4-Octyl-N-(4-octylphenyl)-



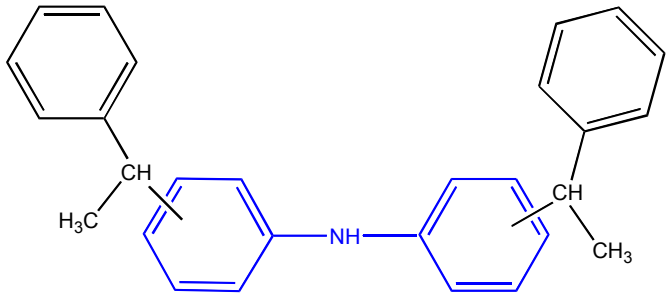
10081-67-1
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]-



68411-46-1
[* Ring attachment at this carbon]

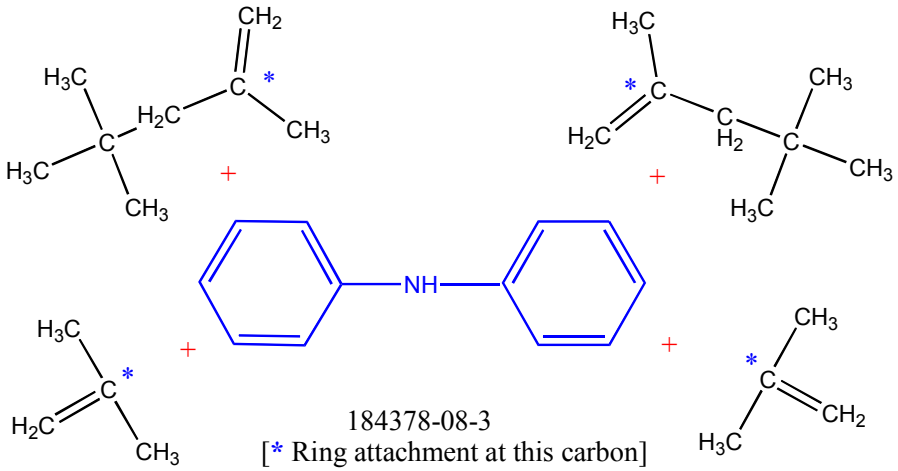
Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene

Figure 2 Substituted Diphenylamine Chemical Structures (continued)



68442-68-2

Benzenamine, N-phenyl-, styrenated

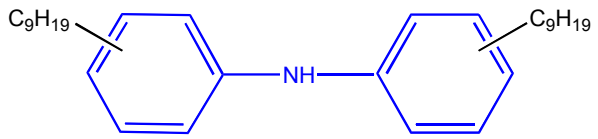


184378-08-3

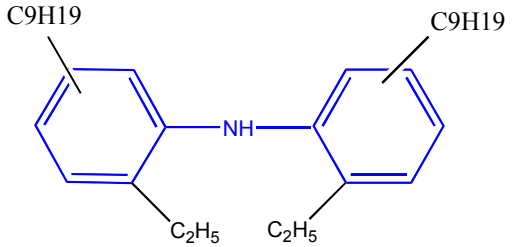
[* Ring attachment at this carbon]

Benzenamine, N-phenyl, reaction products with 2,4,4-trimethylpentene and isobutylene

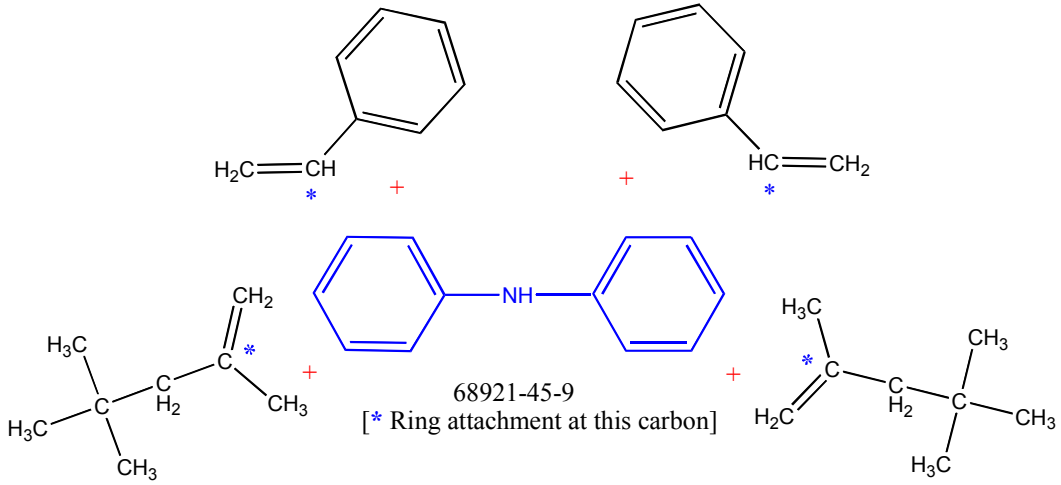
Figure 2 Substituted Diphenylamine Chemical Structures (continued)



36878-20-3
Benzenamine, ar-nonyl-N-(nonylphenyl)-
Mixed Dinonyldiphenylamines



68608-77-5
[alkylation reaction of diethydiphenylamine with propylene trimer]
Benzenamine, 2-Ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives



Benzenamine, N-Phenyl, reaction products with Styrene and 2,4,4-Trimethylpentene

TABLES

Table 1. Justification of the Substituted Diphenylamines Category using Flash Point, Vapor Pressure, Water Solubility and Biodegradation

Name (CAS No.)/ Molecular weight	Substitution	Flash Point (°C)	Vapor Pressure	Water Solubility	Biodegradability
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)/ 298-350	Alkyl	Not determined	2E-5 mm Hg @ 25 °C	Very low	Not determined
Benzenamine, N-phenyl-, styrenated (68442-68-2)/ 320	Aryl	270	<100 hPa @50°C	Very low	Not readily biodegradable
Benzenamine, N-phenyl- (184378-08-3)/225-393[4]	Alkyl	>180	2E-5 mm Hg @ 25 °C	Very low	Not determined
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)/ 394	Alkyl (branched)	Not determined	<0.13332 hPa	Very low	Not readily biodegradable
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1) /406	Aryl	276.7	Not determined	Insoluble	Not determined
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3) / 422	Alkyl (branched)	Not determined	Not determined	Not determined	Not determined
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)/ 225-479	Alkyl	213	2.35E-8 to 9.18E-12 hPa @25C EPIWin	Insoluble	Not determined
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)/ 225-633	Mixed Alky/Aryl	180	9.99E-7 to 1.9E-15 hPa EPIWin	Negligible	Not determined

[4]A major component of CAS number 184378-08-3 is CAS number 68411-46-1.

Table 2. Matrix of Available and Adequate Data on Substituted Diphenylamines Category Members Physicochemical Properties

Name (CAS No.)	Melting Point (°C)	Vapor Pressure (mm Hg @ 20°C)	Boiling Point (°C)	Partition Coefficient	Water Solubility (mg/L)
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	44-107	2E-5 @25 °C	~370 EPIWin	>6	<0.01% @ 20 °C
Benzenamine, N-phenyl-, styrenated (68442-68-2)	~6	<100 hPa @50°C	>300 @1013 hPa	4.64	0.41 @ 20C
Benzenamine, N-phenyl- (184378-08-3)[5]	44-107	2E-5 @25 °C	~370 EPIWin	>6	<0.01%
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	87-95	<0.13332 hPa	200	11.26	<0.1 g/100 ml @21C
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)	98.5	Not determined	Not determined	Not determined	Insoluble
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	Not determined	Not determined	Not determined	Not determined	Not determined
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	Not determined	2.35E-8 to 9.18E-12 hPa @25C	443.18 to 547.61 EPIWin	9.84	2.35E-5 to 5.85E-10 @25C EPIWin
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	Not determined	9.99E-7 to 1.9E-15 hPa EPIWin	>198	5.2	0.3889 to 1.869E-11 @ 25C EPIWin

[5] A major component of CAS number 184378-08-3 is CAS number 68411-46-1.

Table 3. Matrix of Available and Adequate Data on Substituted Diphenylamines Category Members
Environmental Fate

Name (CAS No.)	Hydrolysis	Photo-degradation (t1/2 in hours)	Biodegradation	Environmental Transport
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	Not determined	0.053 hours (EPIWin)	Not determined	Primarily to soil and sediment
Benzenamine, N-phenyl-, styrenated (68442-68-2)	Not determined	Not determined	9% after 28 days	Not determined
Benzenamine, N-phenyl- (184378-08-3)[6]	Not determined	0.053 days (EPIWin)	Not determined	Primarily to soil and sediment
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	Not determined	0.049 days EPIWin	0.78% EPIWin	Primarily to soil and sediment
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)	Not determined	Not determined	Not determined	Not determined
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	Not determined	Not determined	8% after 28 days	Not determined
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	Not determined	0.05 to 0.048 days (EPIWin)	Not determined	Primarily to soil and sediment
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	Not determined	0.051 to 0.053 days (EPIWin)	Not determined	Primarily to soil and sediment

[6] A major component of CAS number 184378-08-3 is CAS number 68411-46-1.

Table 4. Matrix of Available and Adequate Data on Substituted Diphenylamines Category Members Ecotoxicity

Name (CAS No.)	Acute Fish 96-hour LC50 (mg/l)	Acute Invertebrate 48-hour EC50 (mg/l)	Algal growth inhibition EC50 (mg/l)
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	Not determined	Not determined	Not determined
Benzenamine, N-phenyl-, styrenated (68442-68-2)	920	Not determined	Not determined
Benzenamine, N-phenyl- (184378-08-3)[7]	Not determined	Not determined	Not determined
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	>1000	7.7	>100 (growth rate)
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)	Not determined	Not determined	Not determined
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	>10,000	733	600 (growth rate)
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	Not determined	Not determined	Not determined
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	Not determined	2.3 (96 hrs) mysid shrimp	Not determined

[7] A major component of CAS number 184378-08-3 is CAS number 68411-46-1.

Table 5. Matrix of Available and Adequate Data on Substituted Diphenylamines Category Members
Acute Toxicity

Name (CAS No.)	Acute Oral (mg/kg)	Acute Dermal (mg/kg)
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	Not determined	Not determined
Benzenamine, N-phenyl-, styrenated (68442-68-2)	>20,000	>10,000
Benzenamine, N-phenyl- (184378-08-3)[8]	>2500	Not determined
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	>7940	>7940
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)	Not determined	Not determined
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	Not determined	Not determined
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	>34,600	>3000
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	Not determined	Not determined

[8] A major component of CAS number 184378-08-3 is CAS number 68411-46-1.

Table 6. Matrix of Available and Adequate Data on Substituted Diphenylamines Category Members Genotoxicity

Name (CAS No.)	Genotoxicity (*in vitro* bacterial)	Genotoxicity (*in vitro* mammalian)	Genotoxicity (*in vivo*)
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	Not determined	Not determined	Not determined
Benzenamine, N-phenyl-, styrenated (68442-68-2)	Negative	Not determined	Negative
Benzenamine, N-phenyl- (184378-08-3)[9]	Negative	Not determined	Not determined
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	Negative	Negative	Ambiguous
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)	Not determined	Not determined	Not determined
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	Not determined	Not determined	Not determined
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	Negative	Not determined	Not determined
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	Negative	Not determined	Not determined

[9]A major component of CAS number 184378-08-3 is CAS number 68411-46-1.

Table 7. Matrix of Available and Adequate Data on Substituted Diphenylamines Category Members Health Effects

Name (CAS No.)	Repeat Dose	Reproductive	Developmental
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	Not determined	Not determined	Not determined
Benzenamine, N-phenyl-, styrenated (68442-68-2)	Not determined	Not determined	Not determined
Benzenamine, N-phenyl- (184378-08-3)	Not determined	Not determined	Not determined
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	Not determined	Not determined	Chicken Embryos, NOEL 1 uMol/egg
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)	Not determined	Not determined	Not determined
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	Not determined	Not determined	Not determined
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	Not determined	Not determined	Not determined
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	64 week rat dietary study LOEL = 2500 ppm	Not determined	Not determined

Table 8
Substituted Diphenylamines Category Test Plan

CAS Nos. 68411-46-1, 68442-68-2, 184378-08-3, 101-67-7, 10081-67-7
36878-20-3, 68608-77-5 and 68921-45-9
Rubber and Plastic Additives Panel, American Chemistry Council
Revised August 2003

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
A(Calc)	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NA	Not applicable due to physical/chemical properties

	Physical-Chemical				
CHEMICAL	**Melting Point**	**Boiling Point**	**Vapor Pressure**	**Partition Coefficient**	**Water Solubility**
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	A	A	A	A	A
Benzenamine, N-phenyl-, styrenated (68442-68-2)	A	A	A	A	A
Benzenamine, N-phenyl- (184378-08-3)[10]	A	A	A	A	A
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	A	A	A	A	A
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]- (10081-67-1)	A	Test	R	R	R
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	Test	Test	R	R	R
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	Test	A	A	A	A
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	Test	A	A	A	A

[10] A major component of CAS number 184378-08-3 is CAS number 68411-46-1.

Table 8 (continued)

CHEMICAL	Environmental Fate			
	Photodegradation	Hydrolysis	Environmental Transport	Biodegradation
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	A(Calc)	NA	A(Calc)	R
Benzenamine, N-phenyl-, styrenated (68442-68-2)	R	NA	R	A
Benzenamine, N-phenyl- (184378-08-3)	A(Calc)	NA	A(Calc)	R
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	R	NA	A	A
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]- (10081-67-1)	R	R	R	R
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	R	NA	R	A
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	A(Calc)	NA	A(Calc)	R
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	A(Calc)	NA	A(Calc)	R

Table 8 (continued)

CHEMICAL	Ecotoxicity		
	Acute Toxicity to Fish	Acute Toxicity to Algae	Acute Toxicity to Aquatic Invertebrates (e.g., Daphnia)
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	R	R	R
Benzenamine, N-phenyl-, styrenated (68442-68-2)	A	R	R
Benzenamine, N-phenyl- (184378-08-3)	R	R	R
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	A	A	A
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)	R	R	R
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	A	A	A
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	R	R	R
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	R	R	R

Table 8 (continued)

CHEMICAL	Toxicity						
	Acute Toxicity	**Genetic Toxicity *In Vitro* (bacterial)**	**Genetic Toxicity *In Vitro* (mammalian)**	**Genetic Toxicity *In Vivo***	**Repeat Dose Toxicity**	**Repro-ductive Toxicity**	**Develop-mental Toxicity**
Benzenamine, N-Phenyl-, reaction products with 2,4,4-trimethylpentene (68411-46-1)	R	R	R	R	R	R	R
Benzenamine, N-phenyl-, styrenated (68442-68-2)	A	A	R	A	Test	Test	Test
Benzenamine, N-phenyl- (184378-08-3)	A	A	R	R	Test	Test	Test
Benzenamine, 4-Octyl-N-(4-octylphenyl) (101-67-7)	A	A	A	R	R	R	R
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (10081-67-1)	R	R	R	R	R	R	R
Benzenamine, ar-nonyl-N-nonylphenyl (36878-20-3)	R	R	R	R	R	R	R
Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivatives (68608-77-5)	A	A	R	R	R	R	R
Benzenamine, N-Phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (68921-45-9)	R	A	R	R	A	R	R